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SPECIFIC LEPROUS REACTIONS AND ABNORMAL VACCINIA INDUCED IN LEPERS BY SMALLPOX VACCINATION.[1]

By OSWALD E. DENNEY, Surgeon (R), United States Public Health Service, Medical Officer in Charge, U. S. Marine Hospital No. 66 (National Leprosarium), formerly Chief, Culion Leper Colony, P. I.; and RALPH HOPKINS, M. D., Assistant Professor of Dermatology, Tulane University, and Attending Specialist, U. S. Marine Hospital No. 66, formerly Captain, Medical Corps, U. S. A.

As a prophylactic measure against smallpox, 118 lepers and 105 nonleprous attendants were recently vaccinated in the U. S. Marine Hospital No. 66 (National Leprosarium, Carville, La.). The virus used to vaccinate the lepers and the attendant personnel of the hospital was obtained at the same time from the same commercial laboratory, and the same technique was employed in all instances. The number of cases observed under the same conditions warrants, in the opinion of the writers, the drawing of some conclusions.

Though it may be difficult to state what amount of reaction should accompany a normal, successful vaccination, yet the number of cases observed and the marked departure from the control established by vaccination of the hospital personnel demonstrated quite clearly, it is believed, that vaccinia in the lepers ran an abnormally violent course, evidenced in a majority of cases by excessive local inflammation, necrosis, and ulceration, and accompanied by unusually high fever and even severe prostration.

Appearing coincidently with the symptoms of severe vaccinia, and even in some cases of unsuccessful vaccination, were other manifestations specifically leprous in character. Previous and subsequent daily observation of each individual case has shown that these leprous reactions were unusual departures from the course of leprosy and must be attributed to the effect of the vaccine.

CONTROL VACCINATIONS.

Of the 105 nonleprous employees, 74, or 70.5 per cent, were successfully vaccinated as follows:

52 were successfully vaccinated by the first administration;
6 were successfully vaccinated by the second administration;
13 were successfully vaccinated by the third administration;
3 were successfully vaccinated by the fourth administration;
0 were successfully vaccinated by the fifth administration.

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Vaccinations among the nonleprous attendant personnel ran normal courses without exception, the various stages appearing in proper sequence and at proper intervals; secondary reactions, such as local pain and tenderness, axillary adenitis, malaise, and hyperpyrexia, were not more marked than might be expected in average normal individuals. No case was confined to bed or even seriously incapacitated.

LOCAL VACCINIAL REACTIONS IN LEPERS.

Of the 118 lepers, 79, or 67 per cent, were successfully vaccinated as follows:

36 were successfully vaccinated by the first administration;
24 were successfully vaccinated by the second administration;
15 were successfully vaccinated by the third administration;
1 was successfully vaccinated by the fourth administration;
3 were successfully vaccinated by the fifth administration;
0 were successfully vaccinated by the sixth administration.

The local reaction to vaccination in the lepers pursued an atypical course, variable in intensity, but abnormally severe in most cases, and in 11 instances resulted in alarming symptoms. In the more severe cases during the stage of pustulation the areola surrounding the site of inoculation became markedly intensified and grew rapidly in extent. In the course of a few days the inflammation spread over the entire arm. The resulting pain and enormous swelling demanded absolute rest in bed with immobilization of the vaccinated arm for more than one week. The involved areas could not be differentiated clinically from leprous macules undergoing inflammatory changes, such as occur periodically in some cases of maculo-tubercular leprosy, and the "Hansen bacillus" was readily demonstrated in scrapings from the inflamed tissues. The inflammatory crisis was reached in two or three weeks, when gradual return to normal took place. Temperatures ran from 39° C. to 40.4° C., and continued for from one to three weeks.

The vaccination proper progressed from the papular, through the vesicular, to the pustular stage in an apparently normal manner; but frequently the process failed to proceed to normal desiccation and continued as one of necrosis, spreading in a serpentine manner, eventually covering areas from 5 to 15 centimeters in diameter. In from one to two months the resulting ulcers healed by granulation and cicatrization.

Illustrative case.—E. M., No. 53, white male, 59 years of age, mixed type with skin lesions predominating, presenting typical macules generally distributed over trunk and limbs, distinct nodules and deeply infiltrated patches on face, but no gross disfigurement. Some anesthesia but no muscular atrophy or contractures of flexor tendons.

General condition excellent, permitting daily performance of routine duties as a hospital orderly. Since admission to the hospital, about two years previously, he has shown marked improvement with no tendency to attacks of leprous fever or other symptoms of unfavorable progress.

Successfully vaccinated May 15, 1921. After a period of indefinite malaise, there appeared on the twelfth day a violent reaction, accompanied by hyperpyrexia and an outcropping of tubercles around the site of vaccination. These tubercles became involved in the rapidly spreading vaccination areola; similar lesions appeared in light brown macules, previously existing elsewhere on the same arm; coincidently there was an outcropping of tubercles and erythematous macules on the opposite arm in areas previously quiescent. On the thirteenth and fourteenth days numerous new macules and tubercles appeared on the right wrist in areas previously unaffected by leprosy. The site of vaccination no longer resembled a normal vaccination and appeared as a slough 6 centimeters in diameter (fig. 1), evidently extending deeply into the subcutaneous tissues. There was no evidence of secondary infection, and the lesion was treated without antiseptics and protected from trauma with gauze rings. On the seventeenth day the process appeared to have reached its maximum severity, and desiccation of the lesion began; at the same time, the hyperpyrexia and malaise declined in severity until the twenty-fourth day, when the patient was without discomfort. The newly appeared tubercles and macules disappeared rapidly with coincident desquamation of epithelium (fig. 3). On the thirty-second day of vaccination, the patient had returned to his pre-vaccinated state (figs. 4 and 5), with a surprisingly small amount of scarring resulting from the extensive ulceration and necrosis.

SPECIFIC LEPROUS REACTIONS FOLLOWING SUCCESSFUL VACCINATION.

In some instances the reactions were simple recurrences of old symptoms; in others, the reactions were typically those of leprosy, but entirely new to the individual affected.

For convenience, the systemic reactions among those successfully vaccinated will be described as they appeared in the three main divisions of leprosy—namely, the nodular, the maculo-anesthetic, and the mixed types.

NODULAR TYPE.

Among the lepers of the uncomplicated nodular type there appeared, generally on the fourth day of successful vaccination, marked malaise and an increase in body temperature. On the fifth day the process apparently concentrated on the old leprous lesions, which clearly evidenced an inflammatory reaction, enlarging rapidly, and becoming hard and extremely tender. Subsequently, there occurred an outcropping of similar tubercles and infiltrated patches in areas previously unaffected, while the systemic symptoms attained a severity which was frequently sufficient to render the patient bedfast.

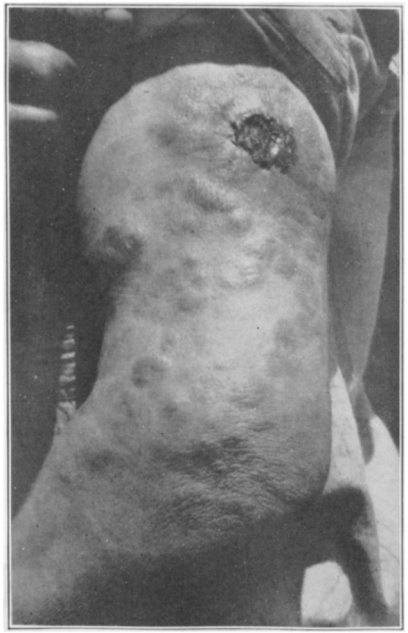
The crisis was usually reached about the twelfth day of successful vaccination, after which a decline of symptoms was noted and the individual rapidly returned to his prevaccinated state.

Illustrative case: C. Y., No. 96, white male, 51 years of age, nodular type. Unsuccessfully vaccinated May 15, 1921; revaccinated May 20. The second vaccination was definitely successful May 24. On the fifth, sixth, seventh, and eighth days, severe malaise and high temperature. On ninth day exhibited considerable inflammatory activity in old tubercles and new tubercles appeared on both arms in areas previously unaffected. On the tenth day the general condition improved, the malaise decreasing, but numerous new tubercles had appeared. On the twelfth day, numerous of the new and old tubercles on his arms underwent resolution and developed into small, cutaneous abscesses. On the thirteenth day about 50 of these abcesses, averaging in size one-half centimeter, were evacuated and swabbed with an antiseptic. The lesions rapidly healed and within two days the patient had returned to his prevaccinated state. Bacterioscopic examination of the material from the evacuated pustules showed numerous leucocytes and myriads of acid-resisting organisms having the morphology of "Hansen bacilli".

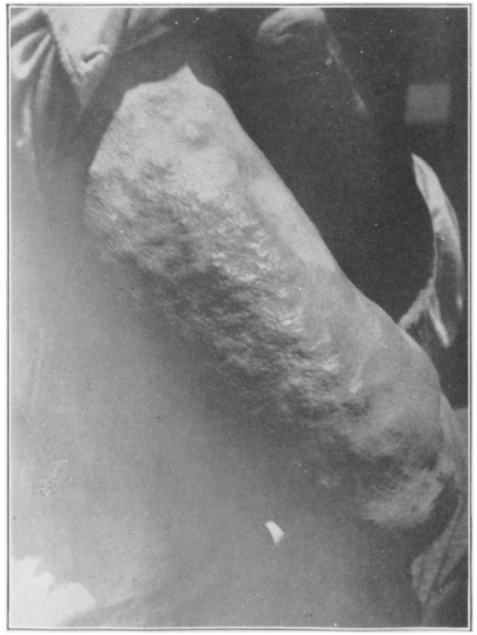
MACULO-ANESTHETIC TYPE.

In the simple, uncomplicated maculo-anesthetic cases, a definite neuritis appeared, usually in the successfully vaccinated arm, frequently in both arms, and rarely in the unvaccinated arm alone. Coincident hyperpyrexia existed, so that the process apparently differed in no respect from the characteristic ulnar neuritis and so-called "leper fever". In three instances the neuritis appeared coincidently in the ulnar and sciatic nerves. In point of time the neuritis ran a much shorter course than that of the nodular types, rarely lasting longer than four days.

Illustrative case: S. H., No. 31, negro woman, 56 years of age, an apparently inactive though advanced anesthetic case, with typical "claw hand" and deformed feet. For a number of years there has been no apparent progression in the disease. Vaccinated May 15, 1921. On the fifth day the vaccination gave promise of success in the papular stage. On the sixth day she complained of violent pain along the course of both ulnar nerves, somewhat more intense in the unvaccinated arm. On the eighth and ninth days the patient still complained of severe pain; the vaccination, however, desiccated rapidly and appeared to have failed of success. May 29, the vaccination having definitely failed, she was revaccinated; the neuritis on this date had practically disappeared. On the sixth day, the vaccination was again apparently successful in the papulo-vesicular stage and the patient again complained of pain, not only along the course of the ulnar but also of the sciatic nerves; the severity of the neuritis was such that morphine was administered to alleviate the suffering. The vaccination again ran an abortive course, the vesicle being completely desiccated by the tenth day, at which time the neuritis had disappeared and the patient had returned to her prevaccinated state.



A.

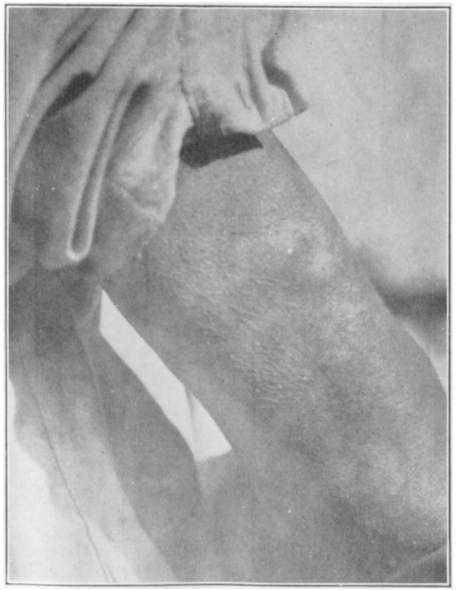


B.

C.

A. Left arm, 12th day after vaccination. Necrotic mass at site of vaccination; numerous new nodules distributed over entire arm. *B.* Right arm, 12th day after vaccination. New nodules so numerous that they are confluent. *C.* Right arm, 23d day after vaccination. Almost complete disappearance of nodules and coincident desquamation. (All of Case 53.)

A.



B.

A. Left arm, six months after vaccination. Complete disappearance of nodules, leaving slightly pigmented areas. Note small cicatrix following vaccinia. *B*. Right arm, six months after vaccination. Small, slightly pigmented macules at sites of former nodules. (Both of Case 53.)

MIXED TYPE.

The mixed cases showed a combination of the reactions described as occurring in the nodular and the maculo-anesthetic types.

Illustrative case: M. S., No. 75, white female, 35 years of age, advanced stage, mixed type of leprosy, with gross disfigurement resulting from both skin and nerve lesions. Vaccinated unsuccessfully May 15, 1921; revaccinated May 20, the papule appeared on the fourth day and proceeded in a normal manner. On the ninth day she began having slight fever, malaise, and arthralgia, which continued with increasing severity, while a painful neuritis developed in the vaccinated arm; coincidently, an inflammatory reaction appeared, involving the same arm from the shoulder to the finger tips. The prostration was so intense that the patient was bedfast for three weeks. The vaccination lesion proper failed to subside on the twelfth day and resulted in a necrotic area which attained in three weeks a diameter of seven centimeters. All the leprous spots over the entire body showed signs of intense inflammation. Numerous new tubercles appeared during the period of prostration. In three weeks the crisis was reached and convalescence began. Some of the newly formed nodules developed into abscesses which, when evacuated, yielded readily to antiseptic dressings and proceeded to complete repair. The necrotic mass at the site of vaccination eventually sloughed, and the lesion healed by granulation and cicatrization at the end of two months, when the patient had not only returned to her prevaccinated state but actually appeared to be in better physical condition than at the time of vaccination.

SPECIFIC LEPROUS REACTIONS FOLLOWING UNSUCCESSFUL VACCINATION.

Thirteen of the lepers who were unsuccessfully vaccinated exhibited reactions similar to, but less intense than, those among the successfully vaccinated, the reaction taking place in response to each administration of the virus.

Illustrative case: D. E., No. 102., white male, 25 years of age, mixed type. Prior to vaccination, the patient was in excellent health, having shown progressive improvement since admission to the hospital. Although formerly subject to ulnar neuritis of the left arm, had been free from attacks for nearly a year. About 10 hours after vaccination of the left arm, on May 15, 1921, he began having ulnar neuritis in that arm. The symptoms rapidly became exaggerated, reaching a crisis in 48 hours. The patient evidently suffered excruciating pain, which changed his habitually cheerful disposition to an irritable, cringing one. He complained of pain which morphine alone appeared to relieve; during the following two days the pain decreased in severity and disappeared. Revaccinations of the left arm on May 20, 24, and 29 caused a recurrence of the same cycle of symptoms, always in the vaccinated arms, so that he had barely recovered from the effects of one vaccination when the next was administered. He evaded the fifth round of vaccinations given to other patients on June 4 and was not revaccinated until June 12, during which interval he completely regained his normal

composure and voluntarily reported for duty as an emergency hospital orderly. His fifth vaccination (June 12) was on his right arm and six hours later he began having ulner neuritis in this arm, which had never previously been affected. The administration of chloral was sufficient to furnish relief during the first 24 hours; as the pain increased during the seven succeeding days it was necessary to give morphine hypodermically to furnish relief. The maximum pain was experienced on the eighth day, after which it declined and disappeared in four days.

SUMMARY.

One hundred and five nonlepers were vaccinated with 74 successful results and with no untoward symptoms.

One hundred and eighteen lepers were vaccinated with 77 successful results. Of the 77 successful vaccinations—

49 had leprous reactions;
2 had leprous reactions and varioloid;
3 had variola; [1]
1 had varioloid; [1]
1 absconded;
4 are cases of presumably arrested leprosy;
17 had no reactions.

Thirty-nine lepers were unsuccessfully vaccinated, and of this number—

13 had leprous reactions in response to each vaccination;
3 had variola; [1]
3 had varioloid; [1]
1 absconded;
5 are cases of presumably arrested leprosy;
14 had no reactions.

COMMENT.

While the exact significance of the phenomena attending vaccinations of lepers is not apparent, the writers feel justified in stating: (A) That the majority of successful vaccinations were abnormally severe in respect to results immediately attributable to vaccine virus; (B) that the normal course of leprosy was profoundly affected by the appearance of definite leprous lesions; and (C) that these lesions were provoked by vaccination and were not merely intercurrent attacks of leprous fever with its usual skin changes.

(A) That the destruction of tissue at the site of vaccination was far in excess of what might be expected in normal individuals under the same conditions was amply evidenced by comparison with the control cases. It is believed that this necrosis was directly due to

[1] The phenomena observed in cases of leprosy affected with smallpox and varioloid will be discussed in a subsequent paper.

vaccine virus and not to secondary infection or to leprous reactions. Secondary infection was eliminated as the causative factor, because no cases of secondary infection with extensive necrosis occurred in the control cases; the leper is well known to be unusually resistant to ordinary staphylococcic and streptococcic infections, even trophic gangrene being less alarming in the leper than in nonleprous individuals; the necrotic areas were dry and the vesicles and pustules before desiccation, though larger than usual, were typically vaccinial; those unsuccessfully vaccinated frequently exhibited considerable local inflammation on the fourth day which seemed to indicate, even in these cases, a susceptibility to some irritant substance in the vaccine. That the necrosis was a leprous manifestation was regarded as improbable for the following reasons: In vaccinating, care was taken to avoid leprous lesions; necrosis and ulceration on the arms are extremely rare in uncomplicated leprosy and occur in terminal cases only; the necrotic areas developed at the site of vaccination only, spread by peripheral extension from the point of inoculation, and, though larger than in normal individuals, in other respects were identical with the more limited necrosis that usually follows vaccination.

(B) It was evident that following vaccination there was a profound systemic disturbance accompanied by unusual skin and nerve lesions identical with the symptoms of leprous fever. That these multiple and generally distributed skin lesions were specifically leprous was shown not only by the clinical characteristics of the lesions but also by repeated bacterioscopic examinations which invariably disclosed great numbers of acid-fast organisms conforming morphologically with the "Hansen bacillus." It is of interest as an indication of symbiosis that in the extensive areola surrounding the site of vaccination there were often found numerous tubercles clinically and bacterioscopically leprous. So intermixed, indeed, were the newly formed leprous lesions and the extensive vaccinial areola that it was often impossible to determine to what extent the resulting enormous swelling of the vaccinated arm was caused by leprosy and to what extent by vaccinia.

(C) It has been noted in a preceding paragraph that the leprous reactions observed following vaccination were identical clinically and bacterioscopically with the spontaneous exacerbations that occur from time to time in uncomplicated leprosy. But the assumption that 51 out of 71 lepers should at a given time spontaneously develop fever and severe acute leprous symptoms is not warranted by the frequency with which these symptoms occur in the usual course of the disease. A proportion as great as five out of seven inmates at the same time suffering from this form of fever is unprecedented in the last 20 years' history of the hospital and can not be explained as

a mere coincidence. That the acute specific leprous lesions described did not occur spontaneously but were induced by vaccination is further evidenced by the uniform time of their appearance after vaccination, by their preponderance near the site of inoculation, and by their occurrence in cases which had not previously and have not subsequently suffered attacks of leprous fever.

In explanation of the phenomena observed, the most satisfactory hypothesis that occurs to the writers is that leprosy and vaccinia are so related that the symptoms of both diseases are exaggerated when lepers are vaccinated. In view of the enormous number of "Hansen bacilli" found, the generally distributed acute leprous lesions must be regarded as the result of unusually rapid proliferation of organisms and can not be explained as a simple foreign protein reaction or shock such as occurs in forms of toxic dermatitis. There seems to exist in chronic leprosy a well-balanced control by which the growth of bacilli is held in check for long periods of years. In spontaneous acute attacks of leprous fever this control seems to be lost, and the probability is that in a similar way vaccinia abolishes inhibiting influences on bacterial growth.

Certain reagents, notably the iodides, ethyl esters of chaulmoogra oil, and various vaccines, including erysipelas and anthrax, may provoke reactions in lepers; the end results of these reactions have been improvement in some lepers and retrogression in others. It is not without interest that in no instance did a case present more pronounced symptoms of chronic leprosy at the subsidence of the acute symptoms provoked by smallpox vaccination, but, on the contrary, some showed actual improvement. It is not improbable that during the acute leprous exacerbation, long acquiescence of the host to bacterial invasion was disturbed, and immunizing substances were produced which were not elaborated during the quiescent periods. The production of such substances in the acute leprous lesions would readily explain the completeness with which such lesions disappeared and also such improvement as has been noted in chronic symptoms. It is with considerable interest, therefore, that observations, to be reported elsewhere, are being made on patients who are now being revaccinated one year subsequent to the observations here recorded.

CONCLUSIONS.

(1) Vaccinia in lepers was accompanied by more severe local symptoms than in normal individuals. This abnormal susceptibility to vaccine virus occurred in all types and stages of leprosy.

(2) Following vaccination, acute specific leprous lesions occurred in a proportion of cases sufficiently large to establish a relationship of cause and effect. These acute leprous reactions developed not

only near the site of vaccination but were generally distributed over the entire body, manifesting themselves as nerve disturbances in the nerve type, as highly inflammatory macules and nodules in the skin type, and as nerve and skin lesions in the mixed type.

(3) The acute leprous reaction to vaccination was of short duration. No case was permanently aggravated, and some showed actual amelioration.

(4) A symbiotic relation existing between vaccine virus and the bacillus of leprosy offers the best explanation of the phenomena observed.

SMALLPOX AND VACCINATION IN DENVER, COLO.

The Department of Health and Charity of Denver, Colo., has issued a leaflet giving information regarding the outbreak of smallpox in that city.

During the 13-month period from November 1, 1921, to November 30, 1922, 854 cases of smallpox, with 263 deaths were recorded. The leaflet contains the names of all patients who died during the months of September, October, and November, 1922.

The accompanying tables have been compiled from the data given in the leaflet.

TABLE 1.—*Vaccination status of smallpox patients, Denver, Colo., November, 1921, to November, 1922, inclusive.*

Month.	Cases.			Fatal cases.[1]		
	Vaccinated.	Not vaccinated.	Total.	Vaccinated.	Not vaccinated.	Total.
1921.						
November	3	43	46	1	10	11
December	18	66	84	3	23	26
1922.						
January	10	62	72	0	24	24
February	9	38	47	5	11	16
March	14	39	53	3	12	15
April	11	34	45	1	18	19
May	10	19	29	0	7	7
June	2	7	9	0	0	0
July	2	9	11	0	3	3
August	2	12	14	0	2	2
September	10	22	32	2	5	7
October	31	129	160	2	39	41
November	60	192	252	6	86	92
Total	182	672	854	23	240	263

[1] Included in "Cases" columns.